AR201-13133A

TEST PLAN FOR SULFOSUCCINATES CATEGORY

June 13.2001

OVERVIEW

The SOCMA Sulfosuccinates Group (SSG) of the Synthetic Organic Chemical Manufacturers Association (SOCMA) hereby submits for review a test plan for a category consisting of three sulfosuccinates under the Environmental Protection Agency's {EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the panel and its member companies to use existing data on one or more of the sulfosuccinates to adequately fulfill the Screening Information Data Set (SIDS) for environmental fate endpoints, ecotoxicity tests, and human health effects for all three sulfosuccinates. The Sulfosuccinates Group believes that adequate data exist to fulfill all the requirements of the HPV program without the need for additional testing.

Test Plan Matrix for Sulfosuccinates

Chemical	Cyclohexyl (CAS # 23386-52-9)	Dimethylbutyl (CAS # 2373-38-8)	Ethylhexyl (CAS # 577-11-7)
PHYSICAL CHEMISTRY			
Melting point	E	E	E
Boiling point	NA	NA	NA
Vapor Pressure	NA	NA	NA
Water Solubility	Y	Y	Y
Kow	E	E	E
ENVIRONMENTAL FATE			
Photodegradation	E	E	E
Stability in Water	E	E	E
Biodegradation	Y	Y	Y
Transport between Environmental Compartments (Fugacity)	E	E	E
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	Y
Acute Toxicity to Aquatic Invertebrates	Y	C	Y
Toxicity to Aquatic Plants	Y	C	C
TOXICOLOGICAL DATA			
Acute Toxicity	Y	Y	Y
Repeated Dose Toxicity	Y	Y	Y
Genetic Toxicity-Mutation	Y	C	Y
Genetic Toxicity-Chromosomal Aberrations	C	C	Y
Carcinogenicity	C	C	Y
Toxicity to Reproduction	Y	Y	Y
Developmental Toxicity	C	C	Y
OTHER TOXICITY DATA			
Human Experience	NR	NR	Y
Pharmacokinetics	NR	NR	Y

Y = adequate experimental data ; NA = not applicable;
E = Endpoint fulfilled via EPIWIN model.
C = endpoint fulfilled by category approach; NR = not required

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1. Information about the Panel

The SOCMA Sulfosuccinates Group is formed under the sponsorship of the Association Management Center at the Synthetic Organic Chemical Manufacturers Association. The Panel consists of the following manufacturers or importers of sulfosuccinates:

Cytec Industries Inc.	MFG Chemical, Inc.
Finetex, Inc.	Rhodia Inc.
McIntyre Group, Ltd.	Uniquema

2. Category Analysis

2.1 Identity of Category Members

The substances included in the Sulfosuccinate Category are as follows:

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt CAS No. 577-l 1-7
Designated as "Ethylhexyl ester."

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt CAS No. 2373-38-8
Designated as "Dimethylbutyl ester."

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt CAS No. 23386-52-9
Designated as "Cyclohexyl ester."

2.2 Background Information on Category Members

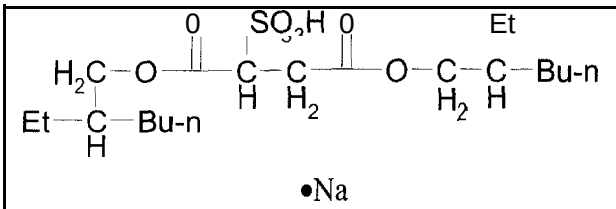
The Sulfosucccinates Category consists of three sulfosuccinate esters as designated above. The molecular structure of all three category members is essentially the same. The general structure for the category is defined as "dialkyl sodium sulfosuccinate" or "dicycloalkyl sodium sulfosuccinate." This describes a molecule with a succinic ester backbone, in which a carbon alpha to one of the carboxyl functions has a sodium sulfo group in place of a hydrogen atom. The only structural difference in the three substances is the alcohol moiety of the ester function. The different alcohol groups are 2-ethylhexyl-, cyclohexyl- and 1,3-dimethylbutyl. The generic molecular structure of all category members is shown below:

$ROOCCH_2CH(SO_3Na)COOR$, Where R = 2-ethylhexyl- $[CH_3(CH_2)_3CH(CH_2CH_3)-]$

= 1,3-dimethylbutyl- $[(CH_3)_2CHCH_2CH(CH_3)-]$

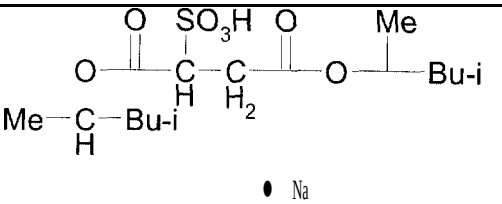
= cyclohexyl- [cyclic $-(CH_2)_5CH-$]

The structures are as follows:



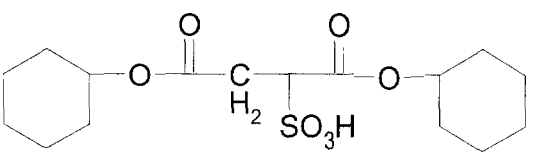
•Na

CAS 577-l 1-7



• Na

CAS 2373-38-8



•Na

CAS 23386-52-9

The three substances are grouped together because of their close structural relationships and the resulting similarities of their physiochemical and toxicological properties. The three sulfosuccinates that are proposed for the category can be used as surfactants or wetting agents, adjuvant in tablets, dispersing or emulsifying agents in foods, and as ingredients in some adhesives, polymeric coatings, detergents, cosmetics and vitamin preparations, They are marketed as solids or solutions in various alcohols.

The ethylhexyl ester is also known as dioctyl sodium sulfosuccinate or docusate sodium. It is generally regarded as safe when used as a stool softener and when used to lower surface tension and produce a mucolytic effect. The usual dosage for these indications is 50 to 2.50 mg daily for adults and children over 12, and 50 to 150 mg for children aged 2-12 (AMA, 1983). As of March 1994, dioctyl sodium sulfosuccinate was reported to be used in 44 cosmetic formulations (FDA, 1994). Concentrations of use are no longer reported to the FDA (Federal Register, 1992). However, FDA data from 1984 report dioctyl sodium sulfosuccinate concentrations in a variety of cosmetics at $\leq$ 5% (FDA, 1984). Dioctyl sodium sulfosuccinate can be used up to 15 ppm in finished gelatin desserts, 10 ppm in finished beverages or fruit juice drinks, 25 ppm in molasses, 25 ppm in non-carbonated beverages containing cocoa fat, 0.5% by weight in gums and hydrophilic colloids, and 9 ppm in finished products when used as a diluent in color additive mixtures for food (CFR, 2000; CIR, 1996).

2.3 Chemical Reactivity and Metabolism

The category members are all chemically stable at room temperature and neutral conditions. They are not particularly sensitive to oxidation, except in the presence of strong oxidizers. They are stable for long periods in aqueous systems, but are expected to undergo saponification (cleavage of the ester groups) in the presence of strong base.

Metabolic studies in animals indicate that the ethylhexyl ester is absorbed and metabolized to some extent after oral administration. Within 24-48 hours of oral administration, 25-35% of ^{35}S-labeled, and 64.1% of ^{14}C-labeled ethylhexyl ester are excreted into urine of rats (Pate1 et al., 1969; Kelly, 1973). Up to 89% of an orally administered dose is excreted into urine of rabbits (Kelly, 1973). The metabolic profile in the rabbit suggests that it is absorbed intact rather than being hydrolyzed in the GI tract prior to absorption. In dogs, 25.5 % and 71 .1% of ^{14}C-labeled ethylhexyl ester is excreted into urine and feces, respectively, suggesting a lower degree of absorption in the dog than the rat (Kelly, 1973). In humans given 100 mg or 200 mg orally, dioctyl sodium sulfosuccinate is present in bile at concentrations of 2-4 x 10^{-5} M (Dujovne and Shoeman, 1972).

From 15.5 to 18.6 % of an orally administered dose (5 to 10 mg) of ^{14}C-labeled ethylhexyl ester to rats is excreted into urine as 2-ethylhexanol-forming compounds. In humans, excretion of 2-ethylhexanol into urine accounts for 2.5-5.0% of an administered dose (200 mg) (Kelly et al., 1973). Therefore, metabolism of the ethylhexyl ester to 2-ethylhexanol is not a major pathway of metabolism in humans.

Based on the data obtained for the ethylhexyl ester and the structural similarities between this chemical and the cyclohexyl and dimethylbutyl esters, it is likely that the cyclohexyl and dimethylbutyl esters are also absorbed to some extent after oral administration. However, since alkyl chains on either of these molecules do not contain the ethyl hexyl moiety, they will not be metabolized to 2-ethylhexanol.

3. Test Plan

3.1 Chemical and Physical Properties

All three category members can be considered organosulfo salts. As neat materials, therefore, they are solids with high melting points, negligible volatility (vapor pressure). When heated above 300" C, they will undergo decomposition instead of boiling. All members are slightly to very slightly soluble in water due to the presence of the sodium sulfo group, which enhances hydrophilicity. However, due to the presence of two 6- and 8-carbon alkyl groups in the ester function, water solubility is limited, and affinity to lipids and hydrophobic materials is enhanced. For this reason, solubility in aqueous media is enhanced by the added presence of water-miscible solvents such as low molecular weight alcohols. Chemical/physical properties are summarized in Table 1.

part solid, part liquid, and will go into solution if a water-miscible organic solvent is present. The solubility of ethylhexyl ester in water is 15 g/l at 25" C, 23 g/l at 40" C, 30 g/l at 50" C, and 55 g/l at 70" C (Windholz, 1983). Water solubility values supplied by the manufacturer for the cyclohexyl ester and dimethylbutyl ester at 25" C are 120 g/l and 300-320 g/l, respectively (Cytec Industries Inc., 2001).

3.1.6 Test Plan for Physical Properties

Pertinent physical property values have been determined either through measurement or estimations using models, such as EPIWIN. No additional determinations are needed.

3.2 Environmental Fate and Pathways

Results of environmental fate studies with the three sulfosuccinates are summarized in Table 2.

Table 2. Environmental fate studies with sulfosuccinates

Endpoint	Cyclohexyl ester, (CAS # 23386-52-9)	Dimethylbutyl ester, (CAS # 2373-38-8)	Ethylhexyl ester, (CAS # 577-l l-7)
Photolysis (Atmospheric $T_{1/2}$)	*5.2 hours*	*7.3 hours*	*5.6 hours*
Photolysis (Hydroxyl Radical Rate Constant)	*24.6 E-12 cm^3/molecule-sec*	*17.4 E-12 cm^3/molecule-sec*	*23.0 E-12 cm^3/molecule-sec*
Stability in Water	*I. 4.5 years @ pH8; 14.5 years @ pH7*	*15.6 years @ pH8; 156 years @ pH7*	*243 days @ pH 8; 6.7 yr @ pH7*
Biodegradation'	35.9% after 28 days (Shake flask)	40.3% after 28 days (Shake flask); 16.7% after 28 days (Closed bottle)	66.7% after 28 days (Closed bottle)
Koc	111	*57.6*	*1040*
Henry's Law Constant	*3.14E-13 atm-m^3/mole (EPI WIN)*	*1.61E-12 atm-m^3/mole (EPIWIN)*	*5.00E-12 atm-m^3/mole (EPIWIN)*

Italicized values are derived from EPIWIN model
'Biodegradation data are for a marketed form of dimethylbutyl ester containing 80% CAS # 2373-38-8, 15% water and 5% ethanol.

3.2.1 Photodegradation

The results of EPIWIN modeling (Table 2) indicate that all three sulfosuccinates are degraded by photolysis to a similar extent.

3.2.2 Stability in Water

The EPIWIN model predicts that these succinate salts are stable to hydrolysis in water with half-lives estimated at several years (Table 2). The dimethylbutyl ester is estimated to hydrolyze more slowly in water than the other sulfosuccinates.

3.2.3 Biodegradation

Results of experiments OECD guideline studies will all three sulfosucccinates also indicate moderate rates of biodegradation. Results of shake flask tests indicate 35.9% biodegradation of the cyclohexyl ester and 40.3% biodegradation of a marketed form of the dimethylbutyl ester after 28 days (United States Testing Company, Inc. 1988a,b). The closed bottle (United States Testing Company, Inc., 199 1 a) test indicates a lower rate of biodegradation of a marketed form of the dimethylbutyl ester (16.7%) than the shake flask test (40.3%). The ethylhexyl ester had a higher rate of biodegradation than the other two sulfosuccinates (66.7% by 28 days in the closed bottle test)(United States Testing Company, Inc., 199 1 b).

A study by Vrbanova et al. (1999) suggests that the initial rates of biodegradation of sulfosuccinate esters increases with increasing length of the alkyl chain up to the C-8 ester, and that the substitution of cyclohexyl for n-hexyl results in a 4-fold decrease in the rate of biodegradation (Vrbanova et al., 1999). Further analyses revealed that the primary factors influencing the rate of biodegradation of linear sulfosuccinates are the number of carbons on the chain (rather than branching) and the degree of hydrophobicity (surfactants with medium hydrophobicity decompose more rapidly than the highly hydrophobic or hydrophilic ones). Based on this analysis, the cyclohexyl and dimethylbutyl esters should degrade more slowly than the ethylhexyl ester. Results of the OECD studies confirm this relationship.

3.2.4 Fugacity

The Mackay Level III fugacity model allows the estimation of relative distributions of chemicals released into the environment, but does not predict actual environmental concentrations. Distributive models, such as the MacKay Level III model, assume zero loss of material through degradation or dispersion out of the environmental system. The MacKay Level III model predicts that all three succinate salts will partition primarily to soil/sediment, some to water and a negligible portion to air (Table 3).

Table 3. MacKay Level III fugacity model

Medium	Cyclohexyl ester (CAS # 23386-52-9)	Dimethylbutyl ester (CAS # 2373-38-8)	Ethylhexyl ester (CAS # 577-l l-7)
	Concentration %	Concentration %	Concentration %
Air	0.875	0.00111	0.287
Water	40.18	27	15.5
Soil	58.2	71.4	46.8
Sediment	0.1	1.68	37.4

The ethylhexyl ester is predicted to partition more to sediment and less to water than the other esters. This is in agreement with the relatively high estimated K_{oc} value of 1040 given in Table 2 for the ethylhexyl ester, as compared with the other two category members. The dimethyl butyl ester is more likely to partition to soil. The very low predicted air concentrations are in agreement with the known negligible volatility of the sulfosuccinate salts, and the low values estimated for the Henry's Law Constants.

3.2.5 Test Plan for Environmental Fate Parameters

All endpoints have been met by experimentation or use of EPIWIN. No further testing is required.

3.3 Ecotoxicity

Results of ecotoxicity studies with the three sulfosuccinates are summarized in Table 4.

Table 4. Ecotoxicity Studies with Sulfosuccinates

Endpoint	Cyclohexyl ester, (CAS # 23386-52-9)	Dimethylbutyl ester, (CAS # 2373-38-8)	Ethylhexyl ester, (CAS # 577-l l-7)
Acute toxicity to fish	96 hr LC_{50} (bluegill) = 470 mg/l	96 hr LC_{50} (bluegill, trout) > 1000 mg/l; 1200 mg/l	96 hr LC_{50} (bluegill, trout) = 37 mg/l; 28 mg/l
Acute toxicity to Daphnia	48 hr EC_{50} = 457 mg/l	ND	48 hr EC_{50} = 36.2 mg/l
Toxicity to algae	No EC_{50} determined Growth stimulated	ND	ND
Phytotoxicity	NOEL (24, 48 hr) =10 mmol/l; 1.25 mmol/l	ND	NOEL (24, 48 hr) = 0.625 mmol/l; < 0.3125 mmol/l
Bioconcentration Factor (BCF)	3.162	3.162	*1.750*

ND = not determined experimentally. Fish toxicity data for the dimethylhutyl ester are for a marketed form containing 80% CAS # 2373-38-8, 15% water and 5% ethanol.
Italicized values designate values obtained by EPIWIN

3.3.1 Acute Toxicity to Fish

Acute toxicity studies in fish have been performed for all three sulfosuccinates. The LC_{50} values for the ethylhexyl ester in two different species of fish range from 28- 37 mg/l (Analytical Biochemistry Laboratories, 1987a, Goodrich et al., 199 1; Goodrich/Huber/Lech, 1985; United States Testing Company, 1990a). The LC_{50} value for the cyclohexyl ester is approximately one order of magnitude higher (470 mg/l)(Analytical Biochemistry Laboratories, 1987b), and the LC_{50} value for a marketed form of the dimethylbutyl ester in two different species is

approximately 1000 g/l (Analytical Biochemistry Laboratories, 1987c; United States Testing Company, Inc. 1990b). The range of LC_{50} values for the sulfosuccinates correlates roughly with the length of side chain.

3.3.2 Acute Toxicity to Aquatic Invertebrates

Data are available for two of the sulfosuccinates (ethylhexyl and cyclohexyl)(GoodrichLech, 1985; Exxon Biomedical Sciences, Inc. 1993a). The 4%hour EC_{50} values for effects on Daphnia for the ethylhexyl ester (36.2 mg/l) and the cyclohexyl ester (457 mg/l) do not differ significantly from their corresponding 96 hr-LC_{50} values determined for fish. Therefore, it is expected that the 48-hour EC_{50} value for exposure of Daphnia to the dimethylbutyl ester would be similar to its 96 hr-LC_{50} value for fish (approximately 1000 mg/l).

3.3.3 Acute Toxicity to Aquatic Plants

Algal toxicity data are available for the cyclohexyl ester. Incubation of Selenastrum capricornutum with 90 mg/l cyclohexyl ester stimulates for 96 hours stimulates growth by 243% (Exxon Biomedical Sciences, Inc, 1993b). Based on the structural similarities between the sulfosuccinates, it is expected that the sodium salts of the ethylhexyl and the dimethylbutyl esters would also stimulate algal growth.

3.3.4 Acute Toxicity to Terrestrial Plants

Data are available for two of the sulfosuccinates (ethylhexyl and cyclohexyl). The toxicity of these sulfosuccinates to Tradescantia bicolor (Wandering Jew) follows the same type of relationship as was observed with fish and Daphnia – the ethylhexyl ester is more toxic (NOEL (48 hr) < 0.3 125 mmol/l) than the cyclohexyl ester (NOEL (48 hr) = 1.25 mmol/l)(Oros et al. 1999). Analyses that Oros and coworkers made with several sulfosuccinic acid esters showed that by decreasing the lipophilicity of the molecules, cyclization and branching of the alkyl chain decreased the toxicity.

3.3.5 Other

The bioconcentration factors (BCF) of the three sulfosuccinates are estimated to range from 1.75 to 3.16, indicating a low potential to bioconcentrate.

3.3.6 Test Plan for Ecotoxicity

No new ecotoxicity testing is recommended. Fish toxicity studies have been performed with ail three sulfosuccinates. Based on the structural similarities of the molecules and the weight of the evidence, the algal and Dapbnia toxicity studies that have been performed on one or two of the sulfosuccinates should suffice for all three.

3.4 Human Health Data

Results of mammalian toxicity tests are summarized in Table 5.

Table 5. Mammalian toxicity of sulfosuccinates

Endpoint	Cyclohexyl ester, (CAS # 23386-52-9)	Dimethylbutyl ester, (CAS # 2373-38-8)	Ethylhexyl ester, (CAS # 577-11-7)'
Acute oral	LD_{50}(rat) = 3.54 g/kg[2]	LD_{50}(rat) = 1.75 g/kg[2]	LD_{50}(rat) = 2 g/kg; 3.08 g/kg; 4.2 g/kg LD_{50}(mouse) = 2.643 g/kg; 4.8 g/kg
Acute dermal	LD_{50}(rabbit) > 5 g/kg[2]	LD_{50}(rabbit) = 5 ml/kg[2] (4 g/kg as contained solids)	LD_{50} (rabbit) > 10 g/kg
Repeated dose (32 day)	NOEL(rat) > 1 .0%[2]	NOEC(rat) > 0.5 %[2]	ND
(90 day)	NOEL(oral rat) > 1 .0% dietarv	NOEL(oral rat) > 1 .0% dietary	NOEL (oral rat) > 1.0% dietary
(16 weeks)	ND	ND	NOEL (oral feed) < 2% dietarv
(26 weeks)	ND	ND	NOEL (oral rat) = 0.5% dietary; LOEL (oral rat) = 1 .O% dietary
(1 year)	ND	ND	NOEL (oral beagle) = 30 mg/kg
Genetic toxicity (in vitro)	Ames test - negative	ND	Ames test - negative CHO cells - positive only at cytotoxic conc.
Carcinogenicity	ND	ND	NOEL (oral rat) = 0.5% dietary; LOEL (oral rat) = 1 .O% dietary; reduced weight gain
Reproductive toxicity	NOEL (oral rat) > 1 .O% dietary for reproductive organs	NOEL (oral rat) > 1 .0% dietary for reproductive organs	NOEL (oral rat) = > 1% dietary for reproductive organs; 1 .0% dietary for reproductive effects; < 0.5% dietary for lactation
Developmental toxicity	ND	ND	NOEL (oral rat) = 1.0% dietary; LOEL (oral rat) = 2.0% dietarv

ND = not determined

'Also referred to as dioctyl sodium sulfosuccinate. Data are reported from studies that used "dioctyl sodium sulfosuccinate", but not "n-dioctyl sodium sulfosuccinate"

[2]A marketed form of the material containing 80% CAS # and 6-8% ethanol was used in the study

3.4.1 Acute Toxicity

Oral LD_{50} values have been reported for all three chemicals in the category (dimethylbutyl as marketed form). In rats, the oral LD_{50} values range from 1.75 - 4.2 g/kg, indicating a low degree of oral acute toxicity (American Cyanamid, 1957, 1966, 1969; Olson et al., 1962; Huntingdon Research Center, 1977). Values obtained in mice (2.6 - 4.3 g/kg) (Hopper et al., 1949; Case et al., 1977) and rats (2 - 4.2 g/kg) for the ethylhexyl ester are similar. There is no significant difference between the LD_{50} values for all three compounds, indicating a similar degree of acute oral toxicity.

Dermal LD_{50} values also have been reported for all three chemicals in the category. The values range from 5 ml/kg (4 g/kg) for a marketed form of the dimethylbutyl ester, to > 10 g/kg for the ethylhexyl ester, indicating a low degree of dermal acute toxicity (American Cyanamid, 1957, 1969; Huntingdon Research Center, 1977; Vernon et al. 1990).

3.4.2 Repeated Dose Toxicity

Oral repeated dose toxicity studies have been performed on all three sulfosuccinates. Results of 32-day studies in rats indicate a NOEL of ≥ 1.0% for the cyclohexyl ester and ≥ 0.5% for the marketed form of the dimethylbutyl ester (American Cyanamid, 1957, 1969). The results of 90-day studies in rats indicate NOELs of ≥ 1% dietary for all three sulfosuccinates (Industrial Bio-Test Laboratories, 1969). Longer term oral toxicity studies in rats (16 or 26 weeks) have shown NOELs of < 2% and 0.5%, respectively (Fitzhugh 1948; Taylor 1966). The only effects noted in rats treated with 2% for up to 26 weeks were GI irritation and reduced weight gain. Daily oral administration of 30 mg/kg ethylhexyl ester for 1 year produces no adverse effects in dogs (Case et al., 1977). Taken together, these results suggest that all three sulfosuccinates are fairly well tolerated when administered repeatedly.

3.4.3 Genetic Toxicity

The cyclohexyl ester has been tested for mutagenicity in Salmonella strains TA-98, TA-100, TA- 1530, TA-1535, TA 1538 and WP-2uvrA- in the absence of S9 (American Cyanamid, 1976), and the ethylhexyl ester has been tested in strains TA-98, TA-100, TA-102, TA-1535, TA-1537 and TA- 1538 in the absence and presence of S9 (Bonin and Baker, 1980; Hazelton Microtest, 1993a). The ethylhexyl ester was tested at the highest concentrations that did not produce cytotoxicity. Results of both studies were negative. A chromosomal aberration assay in Chinese Hamster Ovary cells (CHO) has been conducted with the ethylhexyl ester (Hazelton Microtest, 1993b) . In one out of three experiments, 120 micrograms/ml ethylhexyl ester induced significant chromosomal aberrations (241100 cells scored) in the presence of S-9 activation. The majority were abnormalities other than chromosomal gaps. Toxicity at the concentration that produced aberrations (120 µg/ml) was demonstrated as a 62% reduction in mitotic activity. Complete toxicity at doses exceeding 140 µg/ml was observed. In summary, the ethylhexyl ester only produced aberrations at a concentration close to the toxic threshold.

3.4.4 Carcinogenicity

Long-term studies (up to 2 years) in rats with the ethylhexyl ester have shown that a dietary concentration of 1% produces no adverse effects except reduced weight gain (Fitzhugh and Nelson, 1948). Gastrointestinal irritation is noted in rats ingesting 2% ethylhexyl ester in the diet for 2 years, and ingestion of 8% produces severe GI irritation and lethality within a week (Fitzhugh and Nelson, 1948).

3.4.5 Reproductive Toxicity

Two three-generation reproductive toxicity experiments of have been performed on the ethylhexyl ester (American Cyanamid, 1970; Hazleton Laboratories, 1986; Mackenzie et al., 1990). In each of the experiments, a dietary level of 0.5% was shown to affect parental food consumption, parental and fetal body weight of most generations. However, doses of up to 1 .0% had no effect on fertility and gestation. Ingestion of 2.0% ethylhexyl ester in the diet on days 6-16 of gestation is associated with growth retardation in dams and a significant increase in fetal resorptions (Hoechst Roussel, 1976, 1979). In the reproductive toxicity study by American Cyanamid (1970), ingestion of 1% was associated with decreased lactation index of FO and F2 dams and survivability of the F3 generation. In this study, test diet of some of the dams was replaced with regular diet just prior delivery and during lactation, and their offspring were placed on test diets after weaning. With the exception of the Flb pups, no effects of up to 1 .0% ethylhexyl ester on viability, mean weight, or lactation were noted in pups from dams that did not receive DSS during lactation. This suggests that either the ability of dams to produce milk or the taste of the milk was affected by ingestion of ethylhexyl sulfosuccinate during lactation. Evidence to support this hypothesis comes from the finding in the Hazleton study (wherein all dams were given test diet during lactation) of dose-dependent increases in the number of pups with no milk in their stomachs.

Results of 90-day studies show that ingestion of up to 1 .0% of any of the sulfosuccinates in the category has no effect on reproductive organs of male or female rats (Industrial Bio-Test Laboratories, 1969). The fact that decreased weight gain or food consumption were not noted in rats treated with up to 1 .0% dimethylbutyl or cyclohexyl esters in the diets for 90 days indicates that, unlike the ethylhexyl ester, issues associated with palability (i.e. reduced weight gain in dams and lactation in pups) are not likely to be caused by these compounds at this concentration.

3.4.6 Developmental Toxicity

In the three generation reproductive toxicity studies mentioned above, no developmental toxicity was observed in pups born of rats treated with ethylhexyl ester at concentrations up to 1 .0% (American Cyanamid, 1970; Hazleton Laboratories, 1986; Mackenzie et al., 1990). No adverse effects are noted in offspring of rats given 1 .0% ethylhexyl ester in the diet on days 6-l 5 of gestation (Hoechst Roussel, 1976). Ingestion of 2.0% ethylhexyl ester in the diet on days 6-15 of gestation is associated with an increased percentage of malformed fetuses (20% versus 0% in controls (Hoechst Roussel, 1976). Abnormalities in fetuses include exencephaly, spina bifida, microphthalmia, curved or open vertebral columns, and incomplete ossification of various

cranial bones. An additional study performed at 2.0% also indicates that this dose is associated with an increase in skeletal abnormalities (Hoechst Roussel, 1979; Mattison, 1984). The effects noted at this concentration are associated with maternal toxicity as evidenced by growth retardation and a significant increase in fetal resorptions. Based on the available data and the structural similarities of the compounds, it can be surmised that the cyclohexyl and dimethylbutyl esters would also produce maternal and subsequent developmental toxicity at **2.0%.**

3.4.7 Human Experience

A retrospective study on drug use of 6,837 women during pregnancy indicates that use of dioctyl sodium sulfosuccinate during pregnancy is not associated with an increased risk of birth defects in offspring (Jick et al., 1981).

3.4.8 Test Plan for Mammalian Toxicity

Based on the structural similarities of the molecules and the flat repeated dose mammalian toxicity profile for all three sulfosuccinates, tests already performed will be predictive of results for the other sulfosuccinates.

3.5 Conclusion

Physical Properties

As stated in Section 2.2, the three chemical substances that comprise the Sulfosuccinates Category all have a common molecular structure. Each category member has a molecular structure that consists of a succinic ester backbone, in which a carbon alpha to one of the carboxyl functions has a sodium sulfo group in place of a hydrogen atom. The only structural difference in the three substances is the alcohol moiety of the ester functions. The different alcohol groups are 2-ethylhexyl-, cyclohexyl- and 1,3-dimethylbutyl-.

All three category members have similar physical properties. As neat materials they are all solid salts with high melting points, and negligible vapor pressure. Because they are salts, they will degrade when heated to high temperatures (>300° C) and not boil.

Environmental Fate

All three category members are predicted to undergo photolysis in the atmosphere, with half lives estimated to range from 5.2-7.3 hours. All members are predicted to be stable to hydrolysis in neutral water, but will undergo cleavage of the ester group in the presence of strong base. Biodegradation studies indicated that the succinate esters biodegrade at moderate rates. The Log Kows are estimated at 1.76 for the cyclohexyl ester, 3.98 for the dimethyl butyl ester, and 6.10 for the ethylhexyl ester, which correlate roughly with increasing chain length of the alkyl ester group. Water solubility tends to decrease with increasing side chain length, while Koc values (which predict soil mobility) tend to increase with chain length. Thus, the 2-ethylhexyl ester

appears to be the least water soluble, to have the greatest lipophilicity, and (with the highest Koc value) appears to have the least mobility in soil. The predicted Henry's Law constants for the three sulfosuccinates are low (<1 E-8 atm-m^3/mole). That is consistent with the negligible vapor pressure of salts,

The MacKay Level III fugacity model predicts a similar relative environmental distribution for all three category members, indicating negligible distribution to air, moderate distribution to water, and high distribution to soil and sediment.

Ecotoxicity

The ethylhexyl ester is more toxic to aquatic species than the cyclohexyl ester. Based on studies which indicate that the ecotoxicity of the sulfosuccinates is governed by the length of the side chain, the dimethylbutyl ester is expected to behave more like the cyclohexyl ester than the ethylhexyl ester. The bioconcentration factor (BCF) of the three sulfosuccinates are estimated to range from 1.75 to 3.16, indicating a low potential to bioconcentrate.

Mammalian Toxicity

Results of 90-day repeated dose oral toxicity experiments indicate NOELs of > 1 .O% for all three sulfosuccinates. Based on the structural similarities of the molecules and a flat repeated dose toxicity profile, most tests performed on the ethylhexyl ester will be predictive of results for the other sulfosuccinates. It is likely that the inhibition of lactation caused by the ethylhexyl ester at 1 .0% will not be observed with the dicyclohexyl and dimethylbutyl esters because they do not appear to be unpalatable at this concentration.

Summary

In summary, the data provided in the robust summaries and test plan are consistent with the close molecular similarity and identical functional groups of the category members. The data confirm the validity of the Sulfosuccinates Category. No new testing is required.

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5. Appendix 1 - Criteria for listing of robust summaries

Robust summaries for all HPV endpoints were written from all available data with the following exceptions:

Ethylhexyl ester (CAS #577-11-7) - A biodegradation study by Hammerton (1955) was not summarized because its conduct would not meet today's standards. Toxicity studies performed by Benaglia et al (1943) on rats, rabbits, monkeys and dogs and were not summarized because the results were not well documented, the number of animals was not sufficient, or the NOEL was difficult to determine. Results of a study by Hopper et al. (1949) in mice (LD_{50} = 4.8 g/kg) also were not summarized because the conduct of the study would not be acceptable by today's standards. Physical chemistry and fish toxicity data (48 hr LC_{50} in killifish of 6 1.3 mg/l) from CITI also were not included because the primary source of information was unknown. All studies described in these references would be assigned a reliabiiity of 3 (based on the standards of Klimisch et al., 1997).

6. Appendix 2 - Robust Summaries